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Evidence for Increasing Incidence of Abnormalities of the Human Testis: A Review

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Recent reports have suggested that the incidence of genitourinary abnormalities in human males has increased during the past 50 years, including congenital abnormalities such as cryptorchidism and hypospadia, which seem to be occurring more commonly. Also, the incidence of testicular cancer has increased 3- to 4-fold since the 1940s. This increase seems to be worldwide including countries with a very high frequency of testicular neoplasia as well as those in which this cancer is rather uncommon. It has also been postulated that semen quality has been decreasing for the last half century. A recent study showed that the average sperm density has decreased significantly from 113 million/mL in 1940 to 66 million/mL in 1990. The mean seminal volume has also declined, indicating that the decrease in the total sperm count is even more pronounced than the fall in sperm density would indicate. The remarkable increase in frequency of testicular abnormalities over a relatively short period of time may be due to environmental rather than genetic factors. There is an epidemiological link between the occurrence of different testicular abnormalities. Therefore, common prenatally acting etiological factors with adverse effects on the fetal male gonad might be suspected. However, postnatal influences may also have a deleterious effect on male fertility. From the reproductive point of view, an increased impact on the human male gonad is of concern.

Introduction

The testis plays an essential role in the process of human reproduction. Nevertheless, little attention has been paid to the recent warnings coming from different sources pointing to the increasing incidence of male genitourinary abnormalities during the past 40–50 years. Testicular cancer, hypospadias, and cryptorchidism are being detected more frequently, concurrent with a declining semen quality, all of which indicate that pathological conditions of the male reproductive organs are becoming more common. It is the aim of this review to summarize the available knowledge in this area and present some speculations on the possible etiological factors that are adversely affecting the human testis.

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Testicular Cancer

There is no doubt that the incidence of testicular germ cell cancer has been increasing during the last 40–50 years. In Denmark, all cases of neoplasia have been registered in The Danish Cancer Registry since 1943. From the 1940s to 1980s, the incidence of malignant germ cell neoplasia increased by a factor 3–4 (*1*). However, this increase has been noted not only in Denmark, which has a very high frequency of testicular cancer. In countries with somewhat lower incidences such as Scotland (*2*) and the United States (*3*), and even in those where this tumor type is very rare such as Finland (*4*), a similar secular trend has been also observed.

Hypospadias and Cryptorchidism

Nonneoplastic genitourinary abnormalities such as hypospadias and cryptorchidism have also been reported with increasing frequency (*5*). However, these data should be interpreted with caution. Unlike testicular cancer, the diagnostic criteria for hypospadias and cryptorchidism are not well defined, and the reporting of cases may not have been equally efficient over the years.

Based on data from national statistics of notified congenital malformations observed at birth, a rise in the rate

of hypospadias from 0.15% in 1964 to 0.36% in 1983 was observed in England and Wales. Similar increases were also reported from Sweden and Hungary (*5*).

Recent British data indicate a doubling of the hospital discharge rate with a diagnosis of cryptorchidism, from 1.6% of boys born in the 1950s to 2.9% born in the late 1970s (*6*). Such an increase might be due to a change in treatment policy. However, a similar rise in incidence of cryptorchidism was observed in another English study in which identical criteria for diagnosis of cryptorchidism were used in 1960s and in 1980s (*7*).

Semen Quality

Recent reports have suggested that semen quality has declined during the past 50 years (*8–15*). However, these studies examined predominantly groups of selected individuals such as semen donors (*10*), candidates for vasectomy (*8*), or patients from infertility clinics (*11–13,15*). Additionally, the selection of papers analyzed in those review articles was not systematic, implying a risk of bias. Therefore, the validity of the conclusions drawn in these reports is questionable, and only little attention was paid to the warnings regarding the potential serious consequences of deteriorating male fertility. To elucidate this question, a statistical analysis was performed based on a systematic review of the total international literature on semen parameters published between 1930 and 1991.

A search of the *Cumulated Index Medicus*/Current List (1930–1965) and in MEDLINE-Silver Platter (1966–1991) identified a total of 61 papers containing data on semen quality in healthy humans. The data from 14,947 males indicated a significant decline in average sperm density from 113 million/mL in 1940 to 66 million/mL in 1990 (Fig. 1 and Table 1). The mean seminal volume also declined from 3.40 mL to 2.75 mL, which means that the total sperm count decreased even more than that expressed by sperm density.

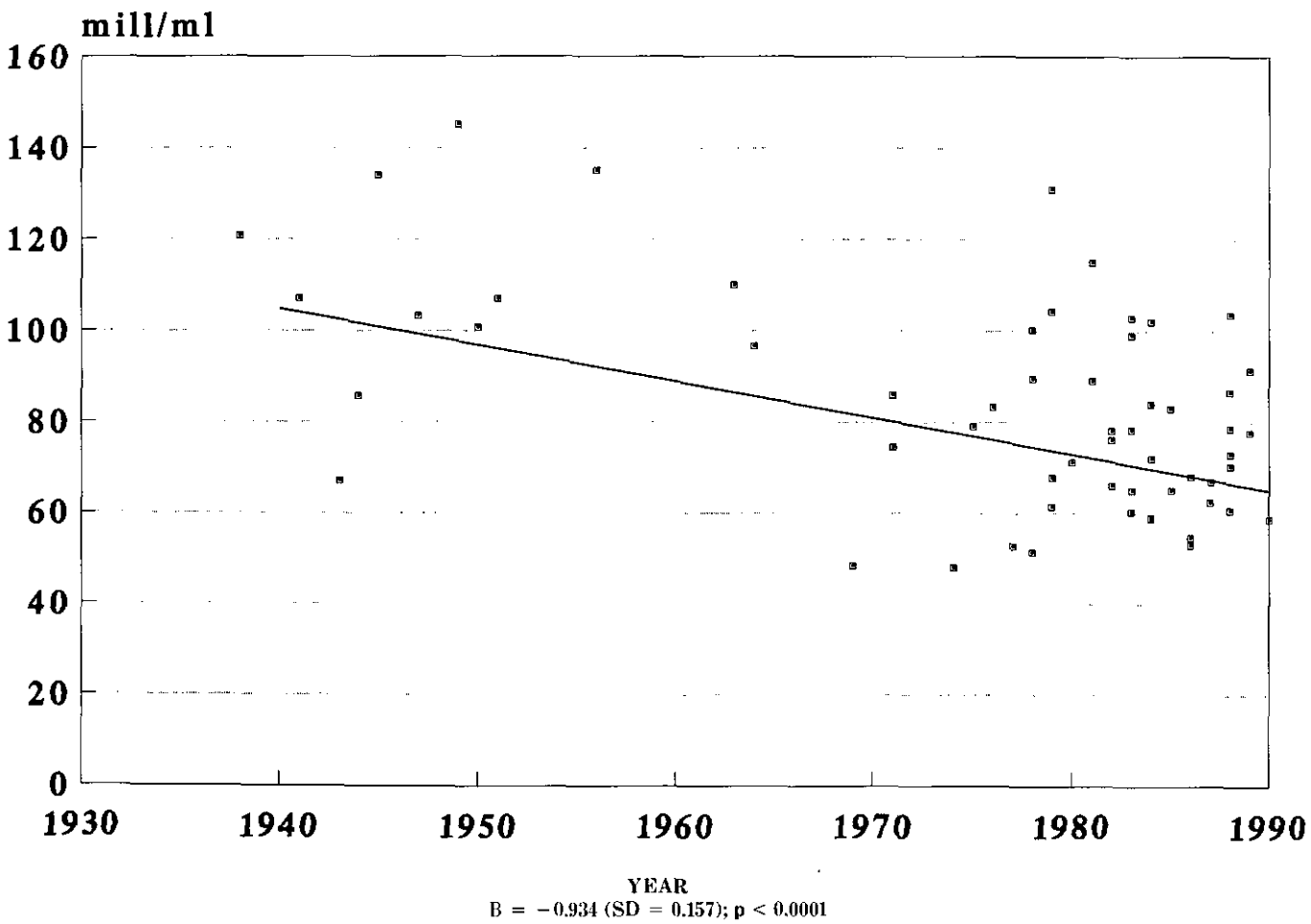

FIGURE 1. Secular trend in sperm density during the period 1938 to 1990. All papers included. Each point represents the mean sperm density in one of the 61 publications used for the analysis. The regression line is also indicated. Each study has been weighted according to the number of subjects included (*99*).

Table 1. Literature values of mean sperm concentration.

First author and reference	Year	Country	Number of men	Mean concentration 10^6 cells/mL	Type[a]
Hotchkiss (*43*)	1938	USA	200	120.63	1
Hotchkiss (*44*)	1941	USA	22	107.00	2
Weisman (*45*)	1943	USA	25	66.90	1
Varnek (*46*)	1944	Denmark	50	85.70	1
MacLeod (*19*)	1945	USA	100	134.00	2
Robles (*47*)	1947	Peru	50	103.20	2
Farris (*48*)	1949	USA	49	145.00	1
Falk (*49*)	1950	USA	100	100.70	1
MacLeod (*50*)	1951	USA	1000	107.00	1
Lampe (*51*)	1956	USA	21	135.00	2
Rutherford (*52*)	1963	USA	100	110.00	1
Zimmerman (*53*)	1964	USA	50	96.60	2
Freund (*54*)	1969	USA	13	48.36	1
Eliasson (*55*)	1971	Sweden	29	85.90	1
Sturde (*56*)	1971	Germany	100	74.43	1
Santomauro (*57*)	1972	USA	79	60.00	1
Nelson (*8*)	1974	USA	386	48.00[b]	1
Naghma-E-Rehan (*58*)	1975	USA	1300	79.00	1
Glaub (*59*)	1976	USA	13	83.20	2
Polakoski (*60*)	1977	USA	7	52.70	2
Brushan (*61*)	1978	India	66	51.36	2
Broer (*62*)	1978	Germany	12	89.50	1
Rehewy (*63*)	1978	USA	33	100.20	1
Nikkanen (*22*)	1979	Finland	21	131.00	2
Roy (*64*)	1979	India	14	104.25	2
Bahamondes (*65*)	1979	Brazil	185	67.64	1
Smith (*66*)	1979	USA	50	61.40	1
Ladipo (*67*)	1980	Nigeria	53	71.20	1
Aabyholm (*68*)	1981	Norway	51	89.00	1
Meyer (*69*)	1981	USA	89	115.00	2
Nieschlag (*70*)	1982	Germany	20	78.00	1
Hamill (*71*)	1982	USA	90	76.00	2
Tjoa (*72*)	1982	USA	4435	66.00	2
Borghi (*73*)	1983	USA	22	60.30	1
Stanwell-Smith (*74*)	1983	UK	38	78.30	1
Osser (*75*)	1983	USA	63	99.10	1
Schwartz (*76*)	1983	France	809	102.90	1
Sultan Sheriff (*77*)	1983	Libya	1500	65.00	1
Handelsman (*38*)	1984	Australia	119	83.90	2
Panidis (*78*)	1984	Greece	114	72.00	1
Lewis (*79*)	1984	USA	9	58.89	1
Swanson (*80*)	1984	USA	36	59.00	1
Laufer (*81*)	1984	Israel	12	102.00	1
Wang (*82*)	1985	Hong Kong	1239	83.00	2
Heussner (*83*)	1985	USA	20	65.00	2
Levin (*84*)	1986	USA	12	68.00	2
Osegbe (*85*)	1986	Nigeria	100	54.65	1
Aribarg (*86*)	1986	Thailand	307	52.90	1
Kirei (*87*)	1987	Tanzania	120	66.90	1
Chan (*88*)	1987	Hong Kong	36	62.40	1
Rasmussen (*21*)	1988	Denmark	14	70.30	2
Giblin (*89*)	1988	USA	28	86.60	2
Welch (*90*)	1988	USA	40	78.60	2
Barratt (*91*)	1988	UK	49	73.00	1
Ibrahim (*92*)	1988	Kuwait	20	60.70	1
Coutinho (*93*)	1988	Brazil	12	103.67	1
Shrivastav (*95*)	1989	UK	15	64.50	1
Badenoch (*95*)	1989	UK	104	91.30[b]	1
Saint Pol (*96*)	1989	France	1222	77.70	1
Sobowale (*97*)	1989	Nigeria	20	87.90	1
Bonde (*98*)	1990	Denmark	54	58.60[b]	2

[a]1, men with proven fertility; 2, normal men of unknown fertility.
[b]Median sperm concentration.

Sperm concentration has been previously shown to correlate with male fertilty (*16*). Other seminal parameters including sperm motility and morphological appearance are also used for evaluation of semen quality. However, the assessment of the two latter parameters may be rather subjective and may therefore differ between laboratories to a greater extent than density measurements (*17*).

It was the conclusion of our study that a genuine decrease in seminal quality had taken place from the 1940s to the 1980s. Further analysis of the data disclosed that the overall decrease was not caused by a deterioration of a subset of ranges of sperm concentration but rather by a general decline in sperm counts (Fig. 2).

Implications of Increased Occurrence of Testicular Abnormalities on Male Fertility

Male fertility is to some extent correlated with the sperm count (*16*). It is noteworthy that the lower reference limit for normal sperm counts has gradually declined from about 60 million/mL in the 1940s (*18,19*) to the present reference level of 20 million/mL (*20*). Furthermore, we showed that the decline in the sperm count from 1938 to 1990 has occurred within all ranges of sperm concentration, which implies that the population of subfertile men may have increased. This may be difficult to document in terms of an altered birth rate, as this is influenced by a wide variety of different factors.

Association between Testicular Abnormalities

Epidemiological Aspects

It is interesting that the data particularly from Denmark and Finland suggest that there is a link between the occurrence of testicular cancer and semen quality. The mean sperm density is much lower in Denmark [70 million/mL (*21*)] than in Finland [131 million/mL (*22*)], and Finnish men have a much lower incidence of testicular cancer than Danish men.

It is well known that the risk of testicular malignancy, invasive germ cell tumor, as well as carcinoma *in situ*, is significantly increased in men with a history of cryptorchidism. Infertility and genitourinary abnormalities such as hypospadias (*23*) may also represent a risk factor for the development of germ cell cancer and testicular cancer may cause reduced fertility and altered secondary sexual characteristics. A significant proportion of men with testicular malignancy have impaired spermatogenesis (*24*). Finally, spermatogenesis and hormone production are both generally impaired in maldescended testes (*25,26*).

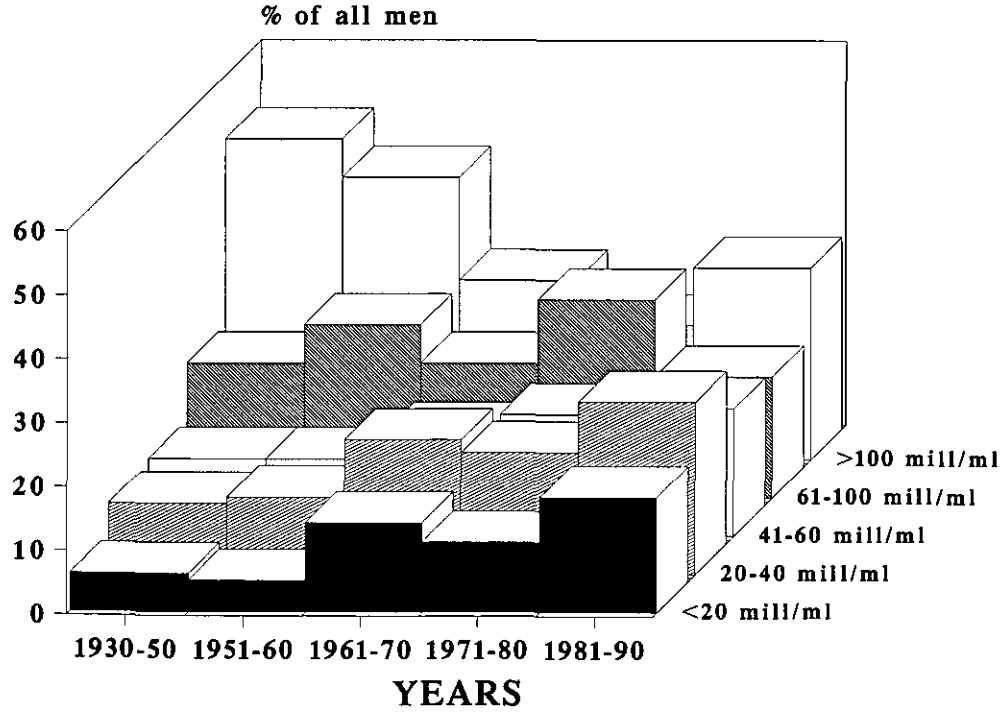

FIGURE 2. Secular trend in percentages of men with sperm density below 20 million/mL, 20–40 million/mL, 41–60 million/mL, 61–100 million/mL or > 100 million/mL. Twenty-seven of the 61 publications contained such data and were therefore included in the analysis (*99*).

Etiological Aspects

The apparent epidemiological association between different testicular abnormalities make it tempting to speculate that they might have a common etiology. Such a hypothesis is strengthened by the fact that not only is cryptorchidism a congenital abnormality but testicular cancer is also thought to have a congenital predisposition because it arises from cells of carcinoma *in situ*, which are assumed to be malignant primordial gonocytes (*27*).

The nature of the possible prenatal factors that have an adverse effect on the testes is still unknown. Estrogens or estrogenlike products have been proposed as factors with deleterious effects on the fetal male gonad (*28–30*). It has also been reported that sons of mothers exposed during pregnancy to diethylstilbestrol may have an increased risk of testicular abnormalities including maldescent and testicular cancer, and a higher percentage of morphologically abnormal sperm cells (*31*). These findings have been confirmed by animal studies (*32,33*). Our knowledge about other factors with a possible similar effect is, however, very limited.

The male gonad may also be adversely affected during adult life (*34*). The hazards may be occupational or other environmental factors or be associated with the lifestyle of the individuals, as discussed elsewhere in the proceedings.

Occupational and Environmental Factors Hazardous to Male Reproduction

Exposure to several physical as well as chemical agents has been suspected as having an effect on human semen quality. For most of these agents the evidence is rather weak and mainly based on animal studies. Furthermore, the results of investigations based on human materials are conflicting. However, there is now rather strong evidence indicating that some of these agents, including ionizing radiation, carbon disulfide, dibromochloropropane, and lead, have an adverse effect on semen quality. The list of substances suspected of influencing the quality of semen is rather long [for review see Schrag and Dixon (*35*) and Henderson et al. (*36*)]. Recently it has been claimed that the higher sperm density found among Hawaiian men as compared to men in the continental part of the United States is due to a lower atmospheric concentration of chemical pollutants (*14*).

The exact relationship between the environment and mean sperm density has not yet been fully elucidated. However, we cannot exclude the possibility that the overall decline in semen quality may be due at least in part to an increased level of various agents in the environment either as occupational hazards in the workplace or as a result of generalized pollution.

Changes in Lifestyle

Smoking and drinking habits as well as sexual behavior have markedly changed over the last 60 years. More promiscuous sexual activity undoubtedly increases the risk of contracting sexually transmitted diseases, which often result in infections of the genital tract, causing lower sperm counts.

The overall cigarette consumption in the United States increased 3- to 4-fold from 1940 to the beginning of the 1980s, although it has since then decreased somewhat (*37*). Smoking has been shown to decrease mean sperm density in some studies (*38*), whereas others (*39,40*) were unable to detect any change. Smoking may have a direct effect on the gonadal function of not only the smoker but also the fetus: an adverse effect on the gonads of the fetus carried by a smoking mother cannot be excluded (*41*).

Ethanol intake has also been increasing over the last 60 years. Although excessive alcohol consumption is known to have adverse effects on spermatogenesis, moderate amounts may not adversely affect male reproductive function (*42*).

Conclusion

Recent data clearly indicate that the semen quality has markedly decreased during the period 1938–1990, and concomitantly the incidence of some genitourinary abnormalities including hypospadias, maldescent, and cancer has increased. Such a remarkable increment in the occurrence of gonadal abnormalities over a relatively short period of time is more likely to be due to environmental rather than genetic factors. Some common prenatal influences could be responsible for both the decline in sperm density and for the increase in hypospadias, cryptorchidism, and cancer of the testis. However, agents acting postnatally may also significantly influence male reproductive function. Generally, it is believed that pollution, smoking, alcohol, and sexually transmitted diseases play a role. To gain more information regarding possible influences on male fertility, it would be valuable to assess semen quality among healthy men in countries with low and high incidences of testicular cancer or in rural as opposed to urban areas. In addition, more research is needed with respect to gonadal function in highly polluted areas. Epidemiological studies on the effect of lifestyle on sperm production or longitudinal, prospective cohort studies may also be valuable.

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